REMARKS/ARGUMENTS

Claims 50, 71-72, 77-88 and 90 are canceled without prejudice to renewal in a subsequently filed application. Claims 91 is added. Therefore, claims 49, 59-70, 89 and 91 are now pending. Support for new claim 91 is found in Fig. 3. Claim 49 was amended for improved clarity. The pending claims are drawn to the embodiment of the invention in which the nucleic acid molecule of the invention encodes a fusion protein having the "bow" configuration of Ang1 (Ang1-FD-Fc-FD). Claim 89 is amended in response to the Examiner's objections. No new matter is added by this amendment.

I. Claim Objections

Claims 89 and 90 were objected to for lack of clarity. Claim 90 is cancelled. In response, claim 89 is amended to provide the definition for the abbreviation "FD". This objection may now be withdrawn.

III. Rejections Under 35 U.S.C. § 103(a)

Claims 49, 50, 59-72 and 77-90 were rejected as obvious over Davis et al. U.S. Patent No. 6,265,564 in view of Sakano et al. US Patent No. 6,337,387. This rejection is respectfully traversed as it may be applied to the currently pending amended claims. Claims 50, 71-72, 77-88 and 90 are canceled.

Analysis of the cited prior art. US 6,265,564 ("the '564 patent") describes fusion proteins containing the fibrinogen-binding domain of Ang1 or Ang2 fused to an Fc domain (Ang1FD-Fc or Ang2FD-Fc) (col. 10, lines 20-27 and 33-39). The FD-Fc fusion proteins are capable of forming dimers composed of two FD-Fc fusion proteins (col. 19, lines 2-6 and Table 1). Example 23 provides the results of experiments with the FD-Fc fusion proteins that show that the monomer form was not able to bind the TIE-2 receptor (col. 44, lines 5-10) and acts as an inhibitor of the receptor (col. 44, lines 23-29).

The '564 patent does not describe or suggest chimeric molecules comprising the "bow" configuration (FD-Fc-FD) as claimed in amended claims 49-50, 59-70, and 89-92.

Sakano et al. describes fusion proteins of human Delta1 or Serrate1 and an Fc domain, and multimers formed by arranging one or more peptides in series or in parallel (col. 16, lines 16-52). Dimers with a higher specific activity are stated to be obtainable.

Sakano et al. does not describe or suggest chimeric molecules comprising the "bow" configuration (FD-Fc-FD) as claimed in amended claims 49-50, 59-70, and 89-92.

Neither of the cited prior art references disclosed the invention as currently claimed, that is,

a "bow" configuration Ang1 (FD-Fc-FD) molecule capable of forming a tetravalent dimeric molecule. Accordingly, it is believed that the Examiner has failed to establish a *prima facie* case of obviousness.

As described in Davis et al. (2003) Nature Structural Biology 10:38-44, the native angiopoietin Ang1 is a TIE-2 receptor activator which is not practically useful as a human therapeutic in spite of its ability to activate TIE-2 because it is heterogeneous in size and composition and difficult to produce and purify recombinantly (Davis et al. 2003 *supra* p.42, second full paragraph). Accordingly, attempts were made to engineer a molecule which would retain the biological activity of Ang1 and overcome the production problems associated with the native molecule.

One prior art approach was to fuse the TIE-2 receptor-binding portion of Ang-1 (the fibrinogen binding domain or "FD") to an Fc domain which would substitute for the native coiled coil domain and allow the molecule to form dimers (the '564 patent). It was expected that an FD-Fc dimer would be able to activate TIE-2. However, that expectation turned out to be wrong – as shown in Davis et al. 2003 *supra*, FD-Fc dimers are antagonists of TIE-2.

Another prior art approach was construction of a chimeric molecule Ang1*, also described in the '564 patent, composed of the N-terminus of Ang2 and the coiled coil and FD domains of Ang1 with the mutation C246S. As shown in Fig.4d of Davis et al. 2003 *supra*, Ang1* forms a tetravalent or higher structure capable of activating the TIE receptor with improved proteolytic stability and purification yield relative to native Ang1. A disadvantage of Ang1* is that it is a heterogeneous composition, forming a mixture of tetrameric and higher order structures.

A new approach is described in the instant specification which is the subject of the presently pending claims. The instant specification describes a fusion protein FD-Fc-FD which forms a homogeneous tetravalent dimeric structure (shaped like a bowtie). Unlike the dimeric FD-Fc, the dimeric FD-Fc-FD is a TIE-2 activator and exhibits a binding affinity to TIE-2 similar to that of Ang1*.

The attached Declaration under 37 CFR 1.132 by Dr. Margaret Karow provides further support of the nonobviousness of the FD-Fc-FD construct forming the tetravalent "bow" molecule. Competition analyses were conducted with six different molecules competing with 1 nM Ang1* for TIE2-Fc binding. The results, summarized in Table 1 of the Declaration, shows that the "bow" molecule exhibits improved TIE-2 binding relative to other constructs, with an IC50 similar to that of Ang1*.

Additionally, pharmacokinetic parameters measured in mice for Ang1* and Ang1-FD-Fc-FD (Table 2) shows that Ang1-FD-Fc-FD has substantially improved pharmacokinetic parameters relative to Ang1*. Accordingly, these results provide support that when tetravalent activating

molecules are compared, the Ang1 "bow" configuration has unexpected properties relative to other molecules, thus overcoming a *prima facie* case of obviousness. It is respectfully requested that in light of the above amendments and remarks, this rejection be withdrawn.

Conclusion

For the above reasons, Applicants contend that all claims are now in condition for allowance, and respectfully request such action.

Fees

This response is filed within the response time set by the Office action dated 02 May 2005, accordingly it is believed that no fee is due. However, if it is determined that a fee is due, authorization is hereby given to charge the amount of any additional fee to Deposit Account No. 18-0650.

Respectfully submitted

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